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Merck Research Laboratories
Worldwide Product Safety

PERIODIC SAFETY UPDATE REPORT FOR:
Finasteride, 1 mg tablet and 0.2 mg tablet, MSD

07-May-2006 to 06-Nov-2006

Periodic Safety Update Report #19

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9.11 Male Reproductive System Symptoms

As per an agency request, spontaneous reports of male reproductive system symptoms[16] in patients on therapy with finasteride 1 mg and 0.2 mg (PROPECIA) were examined for outcome of the event following discontinuation of finasteride therapy. A review of clinical trial data, product labeling and spontaneous reports is provided below.

9.11.1. Clinical Studies

Sexual adverse experiences are defined as untoward effects on sexual function. Data from two Phase III Pivotal studies (087 and 089) which were designed as double-blind, randomized, placebo-controlled, multi-center, 1-year studies in men with mild-to-moderate but not complete male pattern hair loss and which were extended for a further 4 years (four 1-year, placebo-controlled extensions), thus providing placebo-controlled efficacy and safety data through 5 years of treatment, were examined for information regarding sexual adverse experiences and outcomes.

There were 3 sexual adverse experiences found in more than 1% of the finasteride or placebo patients during the 12-month initial studies: decreased libido, ejaculation disorder, and erectile dysfunction. The occurrences of these sexual adverse experiences were followed through the 4 extension studies. Overall, the incidences of drug-related sexual adverse experiences were similar between the finasteride and placebo groups during the extension studies. In total, 72 men on finasteride reported sexual adverse experiences that were considered drug-related by the investigator during the 5 years of the studies. Twenty-four of these men discontinued therapy because of these adverse experiences while 48 remained in the study. Of the 24 men who discontinued, follow-up information is available on 23. Twenty-two men reported resolution of their sexual adverse experience while one reported that the adverse experience was still present 6 months after discontinuing finasteride therapy; however, no further follow-up information is available for this patient. Of the 48 men who reported drug-related sexual adverse experiences and remained in the study, 32 men (56%) reported resolution of their sexual adverse experience while continuing on therapy with finasteride.

9.11.2. Product Labeling

Male reproductive system symptoms are well described in the side effects section of the Company Core Data Sheet (CCDS) as follows:

> PROPECIA is generally well tolerated. Side effects, which usually have been mild, generally have not required discontinuation of therapy. Finasteride for male pattern hair loss has been evaluated for safety in clinical studies involving more than 3,200 men. In three 12-month, placebo-controlled, double-blind, multicenter studies of comparable design, the overall safety profiles of PROPECIA and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 1.7% of

[16] MedDRA terms searched included; ejaculation delayed, ejaculation failure, erectile dysfunction, libido decreased, loss of libido, male sexual dysfunction, organic erectile dysfunction, and sexual dysfunction.

945 men treated with PROPECIA and 2.1% of 934 men treated with placebo. In these studies, the following drug-related adverse experiences were reported in ≥1% of men treated with PROPECIA: decreased libido (PROPECIA, 1.8% vs. placebo, 1.3%) and erectile dysfunction (1.3%, 0.7%). In addition, decreased volume of ejaculate was reported in 0.8% of men treated with PROPECIA and 0.4% of men treated with placebo. Resolution of these side effects occurred in men who discontinued therapy with PROPECIA and in many who continued therapy. The effect of PROPECIA on ejaculate volume was measured in a separate study and was not different from that seen with placebo. The incidence of each of the above side effects decreased to ≤ 0.3% by the fifth year of treatment with PROPECIA.

The following adverse experiences have been reported in postmarketing use: ejaculation disorder; breast tenderness and enlargement; hypersensitivity reactions including rash, pruritus, urticaria, and swelling of the lips and face; and testicular pain.

9.11.3. Background Incidence

The term impotence has historically been defined as "the inability of the male to attain and maintain erection of the penis sufficient to permit satisfactory sexual intercourse".[17] The more precise, [17]and less pejorative, term erectile dysfunction (ED) is now used to signify "an inability of the male to achieve an erect penis as part of the overall multifaceted process of male sexual function". Generally, the terms impotence and erectile dysfunction have been used synonymously in the medical literature.[17]

A cross-sectional multi-national study of the prevalence of ED was conducted on a random sample of approximately 600 men aged 40-70 years for each of the following countries: Brazil, Italy, Japan and Malaysia.[18] Using a standardized questionnaire, ED was assessed by participants' "ability to attain an erection satisfactory for sexual intercourse," and the men were classified as having moderate or complete ED if they answered "sometimes" or "never." The age-adjusted prevalence of moderate or complete ED was 34% in Japan, 22% in Malaysia, 17% in Italy, and 15% in Brazil. Overall age-specific prevalence of moderate or complete ED was 9% for men aged 40-44 years, 12% for 45-49 years, 18% for 50-54 years, and 29% for 55-59 years, and 38% for 60-64 years. In this study, an increased risk for ED was associated with diabetes, heart disease, lower urinary tract symptoms, heavy smoking, and depression and increased by 10% per year of age.

Among 5836 males aged 25-50 years who had undergone medical screening by the Medical services of the Israel Defense Force during 2001-2003 and who completed the Sexual Human Inventory for Males (SHIM) self-administered questionnaire, the prevalence of moderate to severe ED was 7% and 1%, respectively.[19] ED prevalence among young adults was 22.1% among men under 40 years. Severity of ED was correlated with age and diabetes mellitus.

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[17] NIH Consensus Development Panel on Impotence. NIH Consensus Conference: Impotence. *JAMA* 1993; 270 (1): 83-90.

[18] Nicolosi A, Moreira ED, Shirai M, Bin Mohd Tambi MI, Glasser DB. Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. Urology. 2003 Jan;61(1):201-206.

[19] Heruti R, Shochat T, Tekes-Manova D, Ashkenazi I, Justo D. Prevalence of erectile dysfunction among young adults: results of a large-scale survey. J Sex Med. 2004 Nov;1(3):284-91.

Another multinational study interviewed a representative sample of the general male population by age from among 27,839 adult men aged 20-75 years from February 2001 to April 2001 in 8 countries: United States (US, n=9284)), United Kingdom (UK, n=2053)), Germany (n=3040), France (n=2053), Italy (n=2130), Spain (n=1453), Mexico (n=2735) and Brazil (n=5091).[20] The overall prevalence of ED in this study was 16% but varied by country, from a high of 22% of US men to a low of 10% of men in Spain. Prevalence of ED increased with age and was more prevalent among men with cardiovascular disease, hypertension, dyslipidemia, and depression. Prevalence among men less than 40 years was 11% and 8% among men aged 30-39 years and 20-29 years, respectively. Among men who reported ED, 58% had actively sought medical attention for their condition and only 16% of men with ED were currently being treated.

Based on data from the Massachusetts Male Aging Study, a community-based multidisciplinary health and aging survey conducted from 1987 to 1989[21] with subsequent follow-up during 1995 to 1997,[22] the estimated incidence of ED among a sample of 847 men, 40 to 69 years of age (mean age of 52 years) was 25.9 cases per 1,000 man-years. The incidence of ED increased with age and was higher among men with self-reported diabetes and those receiving treatment for heart disease and hypertension. These incidence rates are thought to be conservative estimates of the true rates in the population because follow-up information was missing for a large number of study participants (n = 450). These non-responders were older and differed in characteristics thought to put them at higher risk for ED than those study participants with follow-up information.

9.11.4. Post Marketing experience

The WAES database was searched for spontaneous reports from health care providers, including regulatory agencies, of male reproductive system symptoms[23] in male patients on therapy with finasteride 1 mg tablet (PROPECIA) from market introduction to 06-Nov-2006. A total of 617 reports were identified mapping to the following MedDRA preferred terms, with number of events in parentheses, erectile dysfunction (392), libido decreased (283), sexual dysfunction (86), loss of libido (18), ejaculation failure (9), ejaculation delayed (7), male sexual dysfunction (1), and organic erectile dysfunction (1).

The majority of these reports (93%) were non-serious. Patients ranged in age from 17 -78 years, with the majority of the patients aged 31-50 years. One report (WAES 01015343) identified described a patient who obtained therapy from the internet, thus it is unclear if the patient ever received finasteride therapy, and 4 reports (WAES 0602CAN00131, 0312DEU00092,

[20] Rosen RC, Fisher WA, Eardley I, Niederberger C, Nadel A, Sand M. Men's Attitudes to Life Events and Sexuality (MALES) Study. The multinational Men's Attitudes to Life Events and Sexuality (MALES) study: I. Prevalence of erectile dysfunction and related health concerns in the general population.
Curr Med Res Opin. 2004;20(5):607-17.

[21] Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994; 151: 54-61.

[22] Johannes CB, Araujo A, Feldman HA, Derby CA, Kleinman KP, McKinlay JB. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts Male Aging Study. *J Urol* 2000; 163: 460-463.

[23] MedDRA terms searched included; ejaculation delayed, ejaculation failure, erectile dysfunction, libido decreased, loss of libido, male sexual dysfunction, organic erectile dysfunction, and sexual dysfunction.

0510ITA00002, and 0403USA01479) described patients who developed an adverse experience after therapy with finasteride was discontinued, these 5 reports are not included in the analysis below.

Table 9.11.4.1. describes both action taken with finasteride therapy and the outcome of the adverse experience at the time of the report. It should be noted that in the majority of the reports the adverse experience (AE) information was provided shortly after the onset of the AE and despite attempts to obtain follow up informati on, in accordance with the Company's standard procedures to obtain follow up, no further information was provided. Thus outcome information is limited to what was provided at the time of the report and in most instances long term outcome data is not available.

Table 9.11.4.1.
Action Taken and outcome of the Reported Adverse Experience

	Total	Therapy Discontinued	Therapy Continued	Unknown
Recovered/Recovering	197	154	32	11
Not recovered	200	100	37	63
Unknown	215	-	-	-

In 215 (35%) reports the outcome was unknown, these reports are not discussed further in the analysis below.

Of the remaining 397 reports where an outcome was provided, half (n= 197) described an outcome of recovered/recovering , 11 of these reports were insufficient for further evaluation. Information regarding action taken with finasteride therapy, dose and duration of therapy, concomitant medications, and/or current conditions/medical history was not provided. In 32 of the reports the patients continued on therapy with finasteride and recovered. Three of these reports described concurrent conditions, medical histories and/or other adverse experiences which may have contributed to the patient's adverse experience including diabetes, anxiety and bi-polar disorder. The remaining 154 reports, described patients who discontinued therapy with finasteride and recovered. Twenty-two of these reports described concurrent conditions, medical histories and/or other adverse experiences which may have contributed to the patient's adverse experience including; diabetes, erectile dysfunction, intervertebral disc disorder, depression, hyperprolactinemia, hypogonadism, benign prostatic hyperplasia, alcohol use, hypertension, unspecified psychological "problems" and/or stress, anxiety, and/or inguinal hernia. Of the remaining 132 reports, only 59 desc ribed time to recovery which ranged from 1 day to 4 years with a typical time to recovery of 2-3 months.

In the remaining 200 reports which described the outcome as not recovered, 63 were insufficient for further evaluation. Inform ation regarding action taken with finasteride therapy, dose and duration of therapy, concomitant medications, and/or current conditions/medical history was not provided. In 37 reports the patients continued on therapy with finasteride at the time of the report. Six of these reports described concurrent conditions, medical histories and/or other adverse experiences which may have contributed to the patient's experience including stress, depression, sexual dysfunction, benign prostatic hypertrophy, hypertension, and/or erectile

dysfunction. The remaining 100 reports describe patients whose adverse experience was reported to have persisted upon discontinuation of therapy with finasteride at the time of the report. One quarter (25) of these reports described concurrent conditions, medical histories and/or other adverse experiences which may have contributed to the patient's experience including hypertension, cardiac disease, diabetes, urogenital surgery, hyperthyroidism, sexual dysfunction, anxiety, depression, and/or stress. The majority of the remaining 75 reports lack sufficient information for further evaluation. Information with regards to laboratory, urologic and/or endocrine work up, concurrent conditions/medical history, and/or concomitant therapy is not provided. Most of the reports do not describe how long the event had persisted following discontinuation of finasteride therapy at the time the event was reported. In the few reports, 22, where some information regarding time duration of the events was provided, there was no pattern as to the nature and degree of the adverse experiences, time to onset of the event, and/or length of time the event had persisted following discontinuation of finasteride therapy. The reports described patients with an onset of adverse experiences ranging from 1 week to 4 years and the length of time the events had persisted following discontinuation of therapy, at the time of the report, was typically described as a few months but ranged from weeks to years. Only two of the 72 reports described an endocrine and/or urology work up. These two reports are described in further detail below.

WAES 0602USA01491: a 22 year old male emotionally healthy male with no prior history of sexual dysfunction was placed on therapy with finasteride for the treatment of early male pattern balding. Three to four months later the patient began to experience complete loss of sexual drive, including loss of spontaneous erections. The patient was evaluated by a urologist. Serum testosterone was within normal limits, 567, and testicular ultrasound showed calcifications. Therapy with finasteride was discontinued. Eight months later, the patient reported he continued to experience the same symptoms with no sign of any spontaneous resolution. The patient was evaluated by an internal medicine physician and endocrinologist in addition to the urologist. Diagnostic testing including complete endocrine lab testing, MRI, and serial measurements of testosterone. According to the internal medicine physician, all of the patient's studies have been unremarkable and his testosterone levels continued to be in the 500-700 range. The reporting physician also report that the patients' prescribing physician did not feel that finasteride was causative. No further information was available.

WAES 0501GBR00133: An approximately 19 year old male was placed on therapy with finasteride 1 mg for the treatment of male pattern baldness. There was no concomitant therapy. No information was provided regarding concurrent conditions and medical history. Subsequently the patient experienced erectile dysfunction, gynaecomastia, fatigue and feeling "mentally unclear". Therapy with finasteride was discontinued in May 2003. The patient's experiences persisted. In January 2005 the patient had the following normal laboratory test results: fasting blood sugar 5.5 mmol/l, liver function tests (not further specified), thyroid stimulating hormone 1.9 mu/l, follicle stimulating hormone 2.6 u/l, luteinsing hormone 3.9 u/l, testosterone 17.3 nmol/l, estradiol <100 pmol/l, sex hormone binding globulin 23 nmol/l and dehydroepiandrosterone sulfate 8.3 umol/l. The reporting physician noted that he had no further contact with the patient and presumed he was still waiting for an appointment with endocrinology. The reporting physician felt that

the patient's adverse experiences were ongoing conditions and was "unlikely to have any answers in the near future."

9.11.5. Discussion

Male reproductive system symptoms such as erectile dysfunction and decreased libido are very common with reported incidence rates of 25 per 1,000 man years and are well described in the CCDS.

In clinical trials, the incidences of drug-related sexual adverse experiences were similar between the finasteride and placebo groups during the extension studies. In total, 72 men on finasteride reported sexual adverse experiences that were considered drug-related by the investigator during the 5 years of the studies. Twenty-four of these men discontinued therapy because of these adverse experiences while 48 remained in the study. Of the 24 men who discontinued, follow-up information is available on 23. Twenty-two men reported resolution of their sexual adverse experience while one reported that the adverse experience was still present 6 months after discontinuing finasteride therapy; however, no further follow-up information is available for this patient. Of the 48 men who reported drug-related sexual adverse experiences and remained in the study, 32 men (56%) reported resolution of their sexual adverse experience while continuing on therapy with finasteride

In spontaneous reports analyzed, the age of patients ranged from 17-78 years with the majority of patients aged 31-50. The majority of reports, 93%, were non-serious. In most of the reports the information was provided shortly after the onset of the adverse experience and despite attempts to obtain follow up information, in accordance with the Company's standard procedures to obtain follow up, no further information was provided. In reports where an outcome was provided half described an outcome of recovered/recovering at the time the report was received. In reports where the events persisted, at the time of the report, one third were insufficient for evaluation and 18% of the patients reported continuing finasteride therapy. Of the remaining 100 reports, 25% described concurrent conditions, and/or medical histories which may have contributed to the patient's experiences. In the remaining 75 reports where patients described an adverse experience which persisted after discontinuing therapy with finasteride, at the time of the report, the majority of the reports lacked specific information to allow for further evaluation. No information was provided about the duration of the event following the discontinuation of finasteride and/or no detailed urologic work up was provided. In the few reports which did describe information regarding length of time the events persisted at the time of the report, there was no pattern as to the nature and degree of the event, time to onset of the event and length of time the event persisted following the discontinuation of therapy.

Conclusion

We consider the current labeling as presented in the side effect section of the CCDS to be appropriate and reflective of the extensive data available on finasteride. The Company will continue to monitor reports of persistent male reproductive system symptoms following discontinuation of finasteride therapy.

